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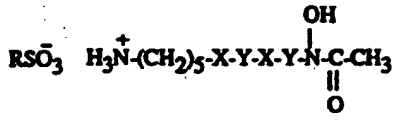

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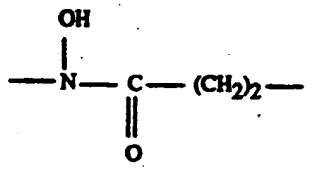

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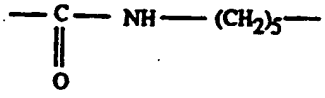

(III)

(57) Abstract

A salt f formula (I) where X den tes a group of formula (II), Y denotes a group f formula (III) and R denotes the residue of an aliphatic or cycl aliphatic sulph nic acid having at least 3 carbon at ms after removal of an -SO_3H group therefr m.

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Desferrioxamine-B salts and their use as orally effective iron chelators

This invention relates to salts of desferrioxamine-B, and to pharmaceutical compositions containing such salts as active ingredients.

The preparations of desferrioxamine-B and pharmaceutically acceptable addition salts thereof are described in U.S. Patent No. 3247197. The amine and salts thereof such as those described in the above mentioned U.S. patent exhibit a marked ability to form stable complexes with trivalent metal ions, especially Fe^{3+}. Consequently, desferrioxamine-B (as the methanesulphonate salt) is of immense importance as a pharmacological iron-chelator in the treatment of iron-overload diseases such as beta-thalassemia. As the only currently marketed drug which is available for the treatment of thalassemia, desferrioxamine-B is vital to the survival of patients suffering from this disease.

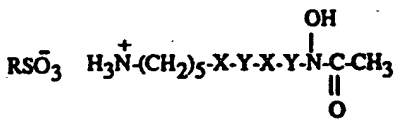
Administration of desferrioxamine-B (as the methane sulphonate salt) via slow (8 to 12 hour) subcutaneous infusion is now widely accepted as the route necessary to control transfusional iron overload in beta-thalassemics. However, such a mode of treatment is laborious, uncomfortable and inconvenient for the patient, and involves high costs. Patient compliance is poor: non-compliance with iron-chelation therapy has been suspected to be the most important cause of death amongst British thalassemics. Hence there is a great need for simpler, more convenient and cheaper iron-chelation therapy, criteria which would be met via an oral dosage form.

This need has been apparent for a long time, and numerous attempts have been made over many years to obtain a form of desferrioxamine-B which is effective in iron-overload therapy when administered orally. Such attempts have included formulations based on the methanesulphonate salt, other known salts and other derivatives. All of these attempts have proved unsuccessful.

It has now been found, in accordance with the present invention, that novel salts of desferrioxamine-B having enhanced lipophilicity provide a means of improving the clinical efficiency of the drug to such an extent that it is effective when administered orally. These salts can exhibit unexpectedly high lipophilicity under physiological

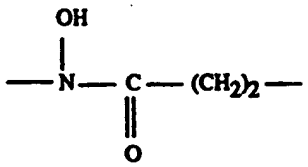
conditions, whilst at the same time having good stability and effective iron-chelating properties.

Accordingly, the present invention provides, in one aspect, a salt of formula



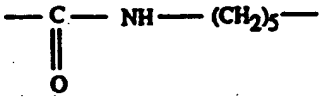
I

where X denotes a group of formula



II

Y denotes a group of formula



(III)

and R denotes the residue of an aliphatic or cycloaliphatic sulphonic acid having at least three carbon atoms after removal of a $-SO_3H$ group therefrom.

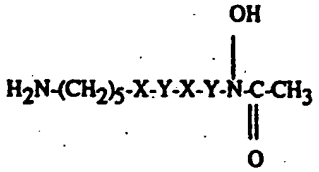
R may contain up to 30 carbon atoms. Preferably it contains at least 6 carbon atoms, more preferably 6 to 20 carbon atoms, especially 6 to 12 carbon atoms, more especially 8 to 12 carbon atoms, most especially 8 to 10 carbon atoms. R may be, for example, a hydrocarbyl group, i.e. the residue after removal of the $-SO_3H$ group from an alphatic or cycloaliphatic hydrocarbyl sulphonic acid, for example an alkanesulphonic, cycloalkanesulphonic, alkenesulphonic or alkynesulphonic acid such as propane-1-sulphonic acid, propane-2-sulphonic acid, butane-1-sulphonic acid, 2-methyl-1-propanesulphonic acid, pentane-1-sulphonic acid, 3-methyl-1-butanesulphonic acid, 2-methyl-1-butanesulphonic acid, pentane-2-sulphonic acid, hexane-1-sulphonic acid, 2-ethyl-1-butanesulphonic acid, 4-methyl-2-pentanesulphonic acid,

hexane-2-sulphonic acid, heptane-1-sulphonic acid, heptane-2-sulphonic acid, octane-1-sulphonic acid, octane-2-sulphonic acid, nonane-1-sulphonic acid, nonane-2-sulphonic acid, decane-1-sulphonic acid, dodecane-1-sulphonic acid, tetradecane-1-sulphonic acid, hexadecane-1-sulphonic acid, octadecane-1-sulphonic acid, cyclopentanesulphonic acid, cyclohexane sulphonic acid, allylsulphonic acid, 2-methyl-2-propene-1-sulphonic acid, hexene-1-sulphonic acid, octene-1-sulphonic acid, decene-1-sulphonic acid, dodecene-1-sulphonic acid, tetradecene-1-sulphonic acid, hexadecene-1-sulphonic acid, cyclopentene-1-sulphonic acid, cyclohexene-1-sulphonic acid, 1,3-cyclohexadiene-1-sulphonic acid, methylacetylene sulphonic acid or decylacetylene sulphonic acid.

In other embodiments of the invention, R may be a substituted hydrocarbyl, usually substituted alkyl group, i.e. the residue, after removal of a SO_3H group, of a substituted hydrocarbyl sulphonic acid, for example a hydroxy-, alkoxy-, acyloxy-, alkoxycarbonyl-, halogen- or amino- substituted alkylsulphonic acid such as 2-hydroxypropane-1-sulphonic acid, 3-hydroxypropane-1-sulphonic acid, 1-hydroxyoctane-2-sulphonic acid, 2-ethoxyethane-1-sulphonic acid, 2-acetoxy-1-butanesulphonic acid, dioctyl sulphosuccinate, 3-chloropropane-1-sulphonic acid, 4-bromobutane-1-sulphonic acid, 1-aminopropane-2-sulphonic acid, 3-aminopropane-1-sulphonic acid, 2-aminopropane-1-sulphonic acid, 1-aminobutane-2-sulphonic acid, 4-aminobutane-1-sulphonic acid or 2-aminobutane-1-sulphonic acid.

Preferably R is the residue of a hydrocarbyl sulphonic acid, especially of an alkanesulphonic acid, after removal of a $-SO_3H$ group therefrom. In specific especially preferred embodiments, R is the residue, after removal of a $-SO_3H$ group, of hexane-1-sulphonic acid, octane-1-sulphonic acid, decane-1-sulphonic acid or dodecane-1-sulphonic acid.

Salts of formula I can be prepared by reacting desferrioxamine-B, i.e. a compound of formula



(IV)

where X and Y are as hereinbefore defined, with a sulphonic acid of formula RSO_3H where R is as hereinbefore defined, or a salt-forming derivative thereof such as a sulphonyl halide, generally using conventional reaction procedures. The salt-forming reaction is conveniently carried out by reacting desferrioxamine-B with a free acid of formula RSO_3H in aqueous methanol, the salt which crystallises being purified by recrystallisation from aqueous methanol or a mixture of water, methanol and acetone. Desferrioxamine-B may be prepared as described in U.S. Patent No. 3 247 197 or U.S. Patent No. 3 153 621.

It has been found that by mixing a salt of the invention as hereinbefore described with another water-soluble salt of a sulphonic acid of formula RSO_3H where R is as hereinbefore defined, a further enhancement of lipophilicity can be achieved. The further water-soluble salt is preferably an alkali metal salt, especially a potassium or sodium salt. This further salt may be used in pharmaceutical compositions in an amount not exceeding its critical micellar concentration. For example, it may be used in an amount up to 50%, such as 0.1 to 50%, by weight of the salt of the invention.

It has also been found that a mixture of desferrioxamine-B methanesulphonate together with a water-soluble salt of a sulphonic acid of formula RSO_3H where R is as hereinbefore defined, which is believed to form a salt of desferrioxamine-B with the acid of formula RSO_3H, i.e. a salt of the invention, under physiological conditions, also exhibits enhanced lipophilicity. The salt of the acid of formula RSO_3H is preferably an alkali metal salt, especially a potassium or sodium salt. This salt may be used in pharmaceutical compositions to provide, together with desferrioxamine-B methanesulphonate, a precursor for a salt of the invention, in an amount not exceeding its critical micellar concentration. For example, it may be used in an amount up to 50%, such as 0.1 to 50% by weight of the desferrioxamine-B methanesulphonate.

The present invention also provides pharmaceutical compositions containing as active ingredient a salt of the invention as hereinbefore described, or a precursor therefor comprising a mixture of desferrioxamine-B methanesulphonate and a water-soluble salt of an acid of formula RSO_3H where R is as hereinbefore defined. Where the composition contains a preformed salt of the invention, the salt may be used in admixture with another water-soluble salt of an acid of formula RSO_3H as hereinbefore described.

Preferred pharmaceutical compositions are those suitable for enteral, especially oral,

administration to warm-blooded animals. Daily dosages may be up to about 4g, for example 500mg to 4g. The compositions may contain the active ingredient alone or in combination with a pharmaceutically acceptable excipient. The compositions may be in dosage unit forms such as tablets, coated tablets, hard or soft gelatin capsules or syrups. These can be prepared using known procedures, for example by conventional mixing, granulating, tablet coating, dissolving or lyophilising processes. Thus, pharmaceutical compositions for oral administration can be obtained by combining the active ingredient with solid carriers, optionally granulating the resulting mixture, and processing the mixture or granulate, if desired or necessary after the addition of suitable excipients, to give tablets or coated tablet cores.

Suitable excipients are, in particular, fillers, such as sugars, for example lactose, sucrose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, and binders, such as starches for example, corn, wheat, rice or potato starch, gelatin, tragacanth, methylcellulose and/or polyvinylpyrrolidone, and/or, if desired, distintegrants, such as the abovementioned starches, and also carboxymethyl starch, cross-linked polyvinylpyrrolidone, agar, alginic acid or a salt thereof such as sodium alginate, and/or flow regulators and lubricants, for example silica, talc, stearic acid or salts thereof such as magnesium stearate or calcium stearate, and/or polyethylene glycol. Coated tablet cores can be provided with suitable coatings, which if appropriate are resistant to gastric juices, using, inter alia, concentrated sugar solutions which may contain gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, shellac solutions in suitable organic solvents or solvent mixtures or, for the preparation of coatings resistant to gastric juices, solutions of suitable cellulose preparations such as acetylcellulose phthalate or hydroxypropylmethylcellulose phthlate. Dyes or pigments can be added to the tablets or coated tablets, for example to identify or indicate different doses of active ingredient.

Other pharmaceutical preparations suitable for oral administration are hard gelatin capsules and also soft sealed capsules made from gelatin and a plasticizer such as glycerol or sorbitol. The hard capsules can contain the active ingredient in the form of granules, for example in admixture with fillers such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate, and if desired, stabilizers. In soft capsules, the active ingredient is preferably dissolved or suspended in a suitable liquid, such as a fatty oil, paraffin oil or a liquid polyethylene glycol, to which a stabiliser can be added.

Salts of formula I in which R contains 8 or more carbon atoms have very low intrinsic dissolution rates in aqueous media, indicating their suitability for the formulation of long acting depot, or other sustained release, dosage forms of desferrioxamine-B.

The present invention also provides pharmaceutically acceptable salts of formula I as hereinbefore described, or precursors therefor as hereinbefore described, for use in a therapeutic method of treating a warm blooded animal body, for the treatment of indications such as aluminium overload, Alzheimer's disease, malaria, reperfusion injury, cancer and particularly in the treatment of iron-overload diseases. The present invention further provides the use of such salts or precursors for the preparation of a pharmaceutical composition for the treatment of the abovementioned indications, particularly iron-overload diseases.

The invention is illustrated by the following Examples, in which parts and percentages are by weight, unless otherwise indicated.

Example 1

A solution of decane-1-sulphonic acid, sodium salt (1.00g, 4.09mmol) in water (100ml) is passed down a column of AG50WX2 cation exchange resin available from Bio-rad (H^+ form, 50ml). The column is washed with water (100ml). The combined eluant is concentrated to 25ml under reduced pressure. The concentrate is added, with stirring, at ambient temperature to a solution of desferrioxamine-B free base (2.24g, 3.99mmol) in 60/40 v/v methanol/water (250ml). The reaction mixture is allowed to stand at ambient temperature for 8 hours. The mixture is concentrated under reduced pressure to 50ml, at which point a white solid crystallises. This is collected by filtration, recrystallised from aqueous methanol and dried under reduced pressure to yield 1.39g (44%) of the decane-1-sulphonate/salt of desferrioxamine-B. Mp 149°C, $C_{35}H_{70}O_{11}N_6S$ Calcd C:53.69%, H:9.01%, N:10.73%, S:4.09%; Found C:53.51%, H:9.01%, N:10.73%, S:4.08%. The homogeneity of the product is confirmed by differential scanning calorimetry (under nitrogen, scan rate 5°C/min, single endotherm at 149°C corresponding to the melting point of the product), and by hplc under the following conditions:- Column: Novapak ODS RCM cartridge available from Waters; Mobile phase: A-Phosphate buffer, pH7.0 containing 4mM nitrilotriacetic acid (NTA), B- 50/50 v/v mixture of buffer A and acetonitrile; Flow rate: 1ml/min; Gradient (Mins/% buffer A): 0/95 20/60 21/60 25/95; Detection: uv/vis at 215nm and 440nm; RT: 20.5 min.

Example 2

Following a procedure analogous to that of Example 1, butane-1-sulphonic acid and desferrioxamine-B are reacted to give the butane-1-sulphonate salt of desferrioxamine-B. Mp 134°C.
$C_{29}H_{58}O_{11}N_6S$ Calcd. C: 49.84%, H: 8.36%, N:12.03%, S:4.59%; Found C:49.52%, H:8.19%, N:12.00%, S:4.14%.

Example 3

Following a procedure analogous to that of Example 1, hexane-1-sulphonic acid and desferrioxamine-B are reacted to give the hexane-1-sulphonate salt of desferrioxamine-B. Mp 138°C. $C_{31}H_{62}O_{11}N_6S$ Calcd C: 51.22%, H:8.60%, N:11.56%, S:4.41%; Found C: 51.04%, H: 8.50%, N:11.40%, S:4.19%.

Example 4

Following a procedure analogous to that of Example 1, octane-1-sulphonic acid and desferrioxamine-B are reacted to give the octane-1-sulphonate salt of desferrioxamine-B. Mp 144°C.
$C_{33}H_{66}O_{11}N_6S$ Calcd C: 52.50%, H:8.81%, N:11.13%, S:4.25%; Found C:52.43%, H:8.75%, N:11.16%, S:4.18%.

Example 5

Following a procedure analogous to that of Example 1, dodecane-1-sulphonic acid and desferrioxamine-B are reacted to give the dodecane-1-sulphonate salt of desferrioxamine-B, Mp 151°C. $C_{37}H_{74}O_{11}N_6S$ Calcd C: 54.79%, H:9.20%, N: 10.36%, S: 3.95%;
Found C: 54.74%, H: 9.15%, N: 10.21%, S: 4.07%.

Examples 6-10

The partition coefficients of the salts prepared in Examples 1 to 5 between n-octanol and water are determined by the 'shake-flask' method f Leo et al, Chem. Rev., 71(6), 525

(1971).

The n-octanol and aqueous phases are mutually saturated prior to conducting the experiment. The desferrioxamine-B sulphonic acid addition salt is dissolved in the aqueous phase at a concentration of 0.005 mol/l and the partition experiment is performed by shaking the vessel containing the two phases until an equilibrium has been achieved. Experiments have revealed that such an equilibrium is set up within 30 minutes shaking - no change in observed partition coefficient is observed if shaking is continued up to 24hours. After equilibrium has been achieved, the sample is centrifuged to enable phase separation. Both organic and aqueous phases are analysed for desferrioxamine-B content via extraction of an appropriate aliquot, quenching with an aqueous (for assay of the aqueous phase) or methanolic (for assay of the n-octanol phase) solution of $FeCl_3$, and measurement of the absorption of the characteristic ferrioxamine-B chelate at ca. 450 nm. Respective calibration plots (absorbance vs. concentration of desferrioxamine-B sulphonic acid salt) for the assay of both aqueous and organic phases show a linear response over the concentration range studied. The results obtained are as follows:

Example	Salt	Partition Coefficient
6	butanesulphonate	0.008
7	hexanesulphonate	0.020
8	octanesulphonate	0.121
9	decanesulphonate	0.366
10	dodecanesulphonate	0.450

Examples 11-15

The partition coefficients of the salts prepared in Examples 1 to 5 between n-octanol and an aqueous phosphate buffer at pH7.4 having an ionic strength of 0.31 mol/l are determined using the procedure of Examples 6-10. The results obtained are as follows:

Example	Salt	Partition Coefficient
11	butanesulphonate	0.006
12	hexanesulphonate	0.010
13	octanesulphonate	0.047
14	decanesulphonate	0.060
15	dodecanesulphonate	0.028

The use of n-octanol/aqueous media partition coefficients as a model for the lipophilicity of drugs is well established (see the abovementioned Leo et al reference). The aqueous phase in Examples 11 to 15 simulates physiological conditions. The results show surprisingly high partition coefficients for salts of the invention in such conditions.

Examples 16-17

Tablets are prepared from the salts of Examples 1 and 4 by compressing a mixture of 99 parts of the salt and 1 part of magnesium stearate in a 13mm die for 2 minutes under a pressure of 4×10^5 kPa. The intrinsic dissolution rates of the tablets are determined using a Langenbucher flow-through apparatus, with water at 25°C as the dissolution medium. The amount of desferrioxamine-B dissolved in the medium is measured at intervals using a spectrophotometric assay at 215 nm. The results obtained are as follows:

Time (min)	% Desferrioxamine-B salt dissolved	
	Ex. 16 (decanesulphonate)	Ex.17(octanesulphonate)
1	1.01	1.71
2	1.65	3.07
5	2.90	6.88
10	4.67	10.56
15	6.17	14.22

20	7.50	17.94
30	9.97	24.73
50	14.21	37.09
75	18.80	48.75
100	22.92	58.34
125	26.62	66.38
150	30.13	72.38
175	33.49	79.13
200	36.85	84.91
225	39.97	89.25
250	42.94	92.50
275	45.87	94.91
300	48.81	96.34

These results show that the intrinsic rate of release of the octanesulphonate and decanesulphonate salts into the aqueous dissolution medium is slow. This can be exploited in the formulation of long-acting depot, or other sustained release dosage forms of desferrioxamine-B.

Examples 18-19

The iron-chelating properties of salts of the invention in a biological system are determined by means of a bioassay in which the growth inhibiting effect of the salts on cells through iron removal is measured by the uptake of radioactively labelled thymidine into the cells. The bioassay is carried out using a Daudi cell line (B-cell lymphoma), a Roswell Park Memorial Institute (RPMI) 1640 medium containing 1μM ferric citrate and supplements as low iron washing medium and RPMI 1640 together with 5% by weight of foetal calf serum as passaging medium.

The cells are fed 24 hours before use. They are washed twice in the low iron washing medium to remove any excess iron and diluted with this medium to a concentration of 0.2×10^6 cells/0.180 ml. To 0.180 ml aliquots are added 0.02 ml of solutions of the desferrioxamine-B salts under test in phosphate-buffered saline (PBS) to give concentrations ranging from a Control containing no salt to a 20μM solution. The cells are then incubated at 37°C in an atmosphere containing 5% by volume of carbon dioxide for 72 hours, being pulsed for the last 8 hours of that time with labelled [^{3}H] Thymidine at 5 micro Ci/ml. The resulting cells are

harvested and their radioactive disintegrations are counted for 10 minutes. The results are shown in the table below as the average of 4 separate experiments (except the Control result in Example 18 which is the average of 3 separate experiments).

Concentration of Salt (μM)	Disintegrations Per Minute	
	Ex 18-octanesulphonate	Ex19-decanesulphonate
20	482	494
15	1065	1101
10	2292	2172
7.5	3716	3262
6	4122	4382
5	5373	5139
4	6280	5445
3	7109	6599
2	7651	6847
1	14765	14161
0.5	21830	23603
0	22297	23897

These results show that as the concentration of the salts of the invention is increased, cell growth is reduced due to removal of iron, thus indicating that the salts of the invention have effective iron-chelating properties in biological systems.

Example 20

The salt of Example 4 (400 parts) is mixed with polyvinylpyrrolidone (8 parts) and sodium lauryl sulphate (3 parts). Sufficient water is incorporated into the mixture to give a cohesive mass, which is passed through a nylon sieve and then dried at 50°C for 3 to 4 hours. The dried mass is resieved and the resulting granules are used to fill size 00 gelatin capsules, each capsule containing 400mg of the salt of Example 4. The filled capsules are coated with a primer coat of a mixture of hydroxylpropyl methylcellulose (10 parts), purified talc (9 parts), Cremophor RH 40 - a solubilising agent available from BASF (0.8 parts), FD & C Red No. 3 vegetable dye (0.2 parts) and purified water (80 parts). The primer coated capsules are coated, using a fluidised bed apparatus, with an enteric coating of a mixture of Eudragit L30D - an anionic polymer available from Dumas Chemicals (32.15 parts),

a polyethylene glycol having a molecular weight of 8000 (1.44 parts), purified talc (1.04 parts), a silicone antifoam emulsion (0.08 parts), ammonia solution (0.05 parts) and purified water (65.24 parts). The resulting enteric-coated capsules are suitable for oral administration.

Example 21

The partition coefficients of the salt prepared in Example 4 and mixtures thereof with sodium octane-1-sulphonate between n-octanol and water are determined using the procedure of Examples 6-10. The salt of Example 4 is dissolved in water at a concentration of 4.5mg/ml. For the mixtures, the sodium salt is mixed with the salt of Example 4 and the mixture is dissolved in the water at 50°C. The results obtained are as follows:

% Sodium Salt by weight of Salt of Example 4	Partition Coefficient
0	0.121
10	0.167
20	0.198
30	0.231
40	0.279
50	0.294

Example 22

Example 21 is repeated using the salt of Example 1 in place of the salt of Example 4, and the sodium salt of decane-1-sulphonic acid in place of sodium octane-1-sulphonate. The results obtained are as follows:

% Sodium Salt by weight of Salt of Example 1	Partition Coefficient
0	0.366
10	0.762
20	0.838
30	1.369
40	1.420

50	1.877

Example 23

The partition coefficients of desferrioxamine-B methanesulphonate and mixtures thereof with sodium decane-1-sulphonate between n-octanol and water are determined using the procedure of Examples 6-10. The methanesulphonate is used at a concentration of 6.0 mg/ml in the water. For the mixtures, the sodium salt is mixed with the methanesulphonate and the mixture is dissolved in the water at 50°C. The results obtained are as follows:

% Sodium Decanesulphonate by weight of Desferrioxamine-B Methanesulphonate	Partition Coefficient
0	0.002
10	0.110
20	0.373
30	0.662
40	0.812
50	1.182

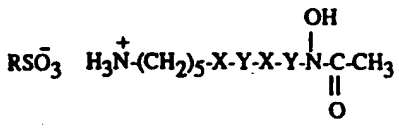
Example 24

Example 23 is repeated, replacing the sodium decane-1-sulphonate used in that Example by sodium octane-1-sulphonate. The results obtained are as follows:

% Sodium Octanesulphonate by weight of Desferrioxamine-B Methanesulphonate	Partition Coefficient
0	0.002
10	0.049
20	0.102
30	0.153
40	0.196
50	0.250

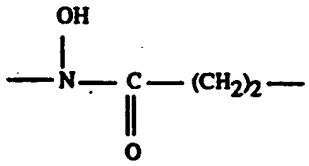
Claims

1. A salt of formula



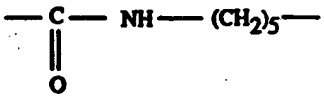
I

where X denotes a group of formula



II

Y denotes a group of formula



(III)

and R denotes the residue of an aliphatic or cycloaliphatic sulphonic acid having at least 3 carbon atoms after removal of a $-SO_3H$ group therefrom.

2. A salt according to claim 1, in which R has at least 6 carbon atoms.

3. A salt according to claim 1, in which R has 6 to 20 carbon atoms.

4. A salt according to claim 1, in which R has 6 to 12 carbon atoms.

5. A salt according to claim 1, in which R has 8 to 12 carbon atoms.

6. A salt according to claim 1, in which R has 8 to 10 carbon atoms.

7. A salt according to any of the preceding claims, in which R is the residue of a hydrocarbyl sulphonic acid after removal of a $-SO_3H$ group therefrom.

8. A salt according to claim 7, in which the sulphonic acid is an alkanesulphonic acid.

9. A salt according to claim 8, in which the sulphonic acid is hexane-1-sulphonic acid, octane-1-sulphonic acid, decane-1-sulphonic acid or dodecane-1-sulphonic acid.

10. A salt of formula I according to any of the preceding claims in admixture with a further water-soluble salt of a sulphonic acid of formula RSO_3H, where R is the residue of an aliphatic or cycloaliphatic sulphonic acid having at least 3 carbon atoms after removal f a $-SO_3H$ group therefrom.

11. A salt according to claim 10, in which R is as defined in any of claims 2 to 9.

12. A salt according to claim 10 or 11, in which the further salt is an alkali metal salt.

13. A salt according to claim 10, 11 or 12, in which the further salt is present in an amount up to 50% by weight of the salt of formula I.

14. A pharmaceutical composition containing as active ingredient a salt according to any f the preceding claims or a mixture of desferrioxamine-B methanesulphonate with a water-soluble salt of an acid of formula RSO_3H where R is as defined in any of claims 1 to 9.

15. A composition according to claim 14, in which said water-soluble salt is an alkali metal salt.

16. A composition according to claim 14 or 15, in which said water-soluble salt is present in an amount up to 50% by weight of the desferrioxamine-B methanesulphonate.

17. A composition according to claim 14, 15 or 16 for oral administration.

18. A composition according to any of claims 14 to 17 which also contains a pharmaceutically acceptable excipient.

19. A salt according to any of claims 1 to 13, or a mixture of desferri xamine-B methanesulphonate with a water-soluble salt of an acid of formula RSO_3H as defined in any of claims 14 to 16, for use in a therapeutic method of treating a warm blooded animal body.

20. The use of a salt according to any of claims 1 to 13, or a mixture of desferrioxamine-B methanesulphonate with a water-soluble salt of an acid of formula RSO_3H as defined in any of claims 14 to 16, for the preparation of a pharmaceutical composition for the treatment of aluminium overload, Alzheimer's disease, malaria, reperfusion injury or cancer.

21. The use of a salt according to any of claims 1 to 13, or a mixture of desferrioxamine-B methanesulphonate with a water-soluble salt of an acid of formula RSO_3H as defined in any of claims 14 to 16, for the preparation of a pharmaceutical composition for the treatment of an iron-overload disease.

22. A method of treating aluminium overload, Alzheimer's disease, malaria, reperfusion injury, cancer or an iron-overload disease which comprises administering a salt according to claim 1 or a pharmaceutical composition according to claim 14 to a warm-blooded mammal in need of such treatment.

23. A process for the preparation of a salt according to claim 1 which comprises reacting desferrioxamine-B with an acid of formula RSO_3H, where R denotes the residue of an aliphatic or cycloaliphatic sulphonic acid having at least 3 carbon atoms after removal of a $-SO_3H$ group therefrom, or a salt-forming derivative thereof.

24. A process for the preparation of a pharmaceutical composition which comprises mixing desferrioxamine-B methanesulphonate with a water-soluble salt of a sulphonic acid f formula RSO_3H where R is as defined in any of claims 1 to 9.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 93/00940

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07C259/06; A61K31/16

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07C

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category *	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	FR,M,1 898 (CIBA SOCIETE ANONYME) 8 July 1963 see page 1, left column, line 1 - right column, line 4 ---	1-24
A	CHEMICAL ABSTRACTS, vol. 94, no. 9, 2 March 1981, Columbus, Ohio, US; abstract no. 58388q, S. T. CALENDER ET AL. 'Iron chelating with oral desferrioxamine' page 75 ; see abstract & LANCET vol. 2, no. 8169, 1980, page 689 --- -/--	1-24

* Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
13 JULY 1993	21. 07. 93
International Searching Authority	**Signature of Authorized Officer**
EUR PEAN PATENT FFICE	SEUFERT G.H.

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	EP,A,0 162 324 (BIORESEARCH) 27 November 1985 see page 2, line 3 - line 9, line 20 - line 31; page 3, line 9 - line 14; page 7, line 5 - line 35 ---	1-24
A	WO,A,8 503 290 (ORAL-D) 1 August 1985 see page 4, line 15 - page 6, line 8; page 11, line 23 - line 33 -----	1-24

INTERNATIONAL SEARCH REPORT

l national application No.

PCT/GB93/00940

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 22 is directed to a method of treatment of the human body, the search has been carried out and based on the alleged effects of the compounds/composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

GB 9300940
SA 73497

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 13/07/93

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
FR-M-1898		FR-M-	1899	
		FR-A-	1315046	
		FR-A-	1315047	
EP-A-0162324	27-11-85	AU-A-	4251785	21-11-85
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		JP-A-	60255799	17-12-85
		SU-A-	1487816	15-06-89
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		CA-A-	1247120	20-12-88
		EP-A,B	0171414	19-02-86
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		US-A-	5047421	10-09-91
		US-A-	4671901	09-06-87